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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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TECH CENTER 1600/2900

In re patent application

No. 09/210,995

Applicant: Sheena M. Loosmore et al

Title: MULTI-COMPONENT VACCINE COMPRISING AT LEAST TWO ANTIGENS FROM HAEMOPHILUS INFLUENZAE TO PROTECT AGAINST DISEASE

Filed: December 15, 1998

Group No. 1641

Examiner: J. Hines

April 13, 2000

RESPONSE UNDER 37 CFR 1.116 – EXPEDITED PROCEDURE

AND REQUEST FOR EXTENSION OF TIME

BY COURIER

The Commissioner of Patents
and Trademarks,
BOX AF,
Washington, D.C. 20231,
U.S.A.

Dear Sir:

This Communication is submitted in response to the Office Action of October 14, 1999.

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of three months of the period for response to the outstanding on this case. We enclose our cheque in the amount of the prescribed fees.

The Examiner noted that the drawings were objected to as set forth in the PTO-948 appended to the Office Action. The Examiner required applicants to submit a proposed drawing correction in reply to the Office Action. The Examiner noted that formal correction of the defects can be deferred until the application is allowed by the Examiner. Submitted herewith is a print of the drawings which applicant expects to submit when the application is allowed. The Examiner is requested to approve these drawings.

The Examiner noted the oath or declaration to be defective, requiring submission of a new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date. The defect in the prior oath or declaration was that Michel Klein did not date the declaration. A newly-executed Declaration and Power of Attorney, identifying this application by application number and filing date will follow shortly. It is submitted that the declaration now complies with 37 CFR 1.67(a).

The specific withdrawal of the rejection of claims 22 to 23 under 35 USC 112, second paragraph, as a result of applicants' amendments, is gratefully acknowledged. The specific withdrawal of the rejection of claims 1 to 5 and 24 under 35 USC 102(a) as being anticipated by Barenkamp et al, is gratefully acknowledged.

While the Office Action does not specifically so state, it is assumed from the narrative in the Office Action that the Examiner is maintaining the prior rejection of claims 1 to 24 under 35 USC 103(a) as being unpatentable over Barenkamp et al (WO 97/36914) in view of Loosmore et al. Reconsideration is requested, having regard to the following comments.

The present invention relates to an immunogenic composition for conferring protection against disease caused by *Haemophilus influenzae*, which comprises at least two different antigens of *Haemophilus influenzae*, at least one of which antigen is an adhesin and the other of which antigen is not an adhesin. The antigen which is an adhesin is preferably a high molecular weight (HMW) protein of a non-typeable strain of *Haemophilus influenzae* while the antigen which is not an adhesin preferably is a non-proteolytic heat shock protein of a strain of *Haemophilus influenzae*.

According to claim 1, a preferred embodiment of the composition contains an analog of *Haemophilus influenzae* Hin47 protein having a decreased protease activity which is less than about 10% of that of natural Hin47 protein and a high molecular weight protein of non-typeable *Haemophilus influenzae*. Claim 7 recites that the HMW protein is present in an amount which enhances the immune response in the host to the Hin47 protein. Claim 8 recites that the HMW protein is present in the recited amount while the individual immunogenicities of the proteins in

the composition are not impaired. The applicants results show that these results can be achieved.

Barenkamp (WO 87/36914) teaches high molecular weight proteins of non-typeable *H. influenzae* identified as HMW1, HMW2, HMW3 and HMW4, which are characterized by molecular weight and sequence information. Loosmore et al teach an analog of *H. influenzae* Hin47 protein with reduced protease activity. It is submitted that these references lack any motivation to combine a non-proteolytic heat shock protein of Loosmore et al with the HMW proteins of Barenkamp et al in an immunogenic composition, particularly in quantities where the immunogenicity of the Hin47 protein is improved by the HMW protein and in which the individual immunogenicities are not impaired.

In the Final Action, the Examiner states:

> "Applicants argues that Barenkamp et al., (WO 97/36,914) provides no suggestion that the High Molecular Weight (HMW) antigens can be used in conjunction with the recited antigens. However, Barenkamp et al., teaches that the HMW protein can be linked to an antigen, hapten or polysaccharide for eliciting an immune response to the antigen, hapten or polysaccharide (page 6 lines 2-5)."

This passage in Barenkamp et al refers to <u>linking</u> the HMW protein to materials with low or no immune response for the purpose of improving that response. It is well known that carrier proteins can be used for this purpose. This disclosure is irrelevant to combining antigens which are already highly immunogenic in an immunogenic composition.

The Examiner goes on to state:

> "Further, Barenkamp et al., teaches that targeting molecules used in combination immunogenic compositions can include fragments of bacterial toxins (page 6 lines 33-34)."

This passage of Barenkamp et al is dealing with formulation of an immunogenic composition containing the HMW protein in combination with a targeting molecule for delivery to specific cells of the immune system. There is no suggestion that the mutant Hin47 protein is a targeting vehicle and hence this passage of Barenkamp is irrelevant.

The Examiner goes on to state, in the Office Action:

> "The immunogenic composition may also comprise at least one other immunogenic or immunostimulating material and at least one adjuvant"

The Examiner is correct that such statement appears in lines 1 to 4 on page 7. However, that is far from any specific teaching to combine mutant Hin47 protein with HMW protein in an immunogenic composition.

The Examiner also states:

> "and teaches complexing additional components to the antigenic composition to enhance immune response including herpes simplex virus vaccine, pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine and hepatitis B virus antigen and others."

As has been pointed out previously, this is an incorrect statement. It is not known why the Examiner persists in this incorrect notion having regard to applicants comments. As previously pointed out, the references to herpes simplex virus vaccine and pseudorabies virus vaccine (page 24, ll. 19 to 21) are made in the context of reporting work done by Lockhoff (USP 4,855,283) using glycolipid analogs as adjuvants, suggesting that such analogs could be used in the HMW containing immunogenic compositions as adjuvants. There is absolutely no suggestion of "complexing additional components to the immunogenic composition" in the form of herpes simplex virus, but rather the possibility of using glycolipid analogs as an adjuvant for the HMW protein is discussed, since it has been used with HSV.

The references to tetanus toxoid and poliomyelitis virus vaccine (page 24, ll. 28 to 30) are in the context of reporting work performed by Maloney (USP 4,258,029) using octadecyl tyrosine hydrochloride (OTH) as adjuvants, suggesting that OTH could be used as an adjuvant in the HMW protein containing immunogenic compositions. There is absolutely no suggestion of combining tetanus toxoid and/or polio vaccine with HMW in an immunogenic composition.

Similarly, the reference to hepatitis B virus antigen (page 24, ll. 31 to 32) is in the context of reporting work performed by Nixon-George et al (ref. 30) using octadecyl esters of aromatic amino acids as adjuvants, suggesting that such material would be used as adjuvants in the HMW protein containing immunogenic compositions. There is absolutely no suggestion of combining hepatitis B virus antigen with HMW in an immunogenic composition.

It is submitted that it is entirely out of context to suggest, as the Examiner does, that, on the basis of these disclosures, HMW protein would be combined with any one or a combination of herpes simplex virus vaccine,

pseudorabies virus vaccine, tetanus toxoid, poliomyelitis virus vaccine and hepatitis B virus antigen in an immunogenic composition. The passages in question in Barenkamp et al are discussing certain materials which may be used as adjuvants in the HMW-containing immunogenic composition, because they have been used in other vaccine formulations with the recited vaccine materials.

The Examiner next states:

> "Barenkamp et al., combined vaccines can contain material from various pathogens or from various strains of the same pathogen, or from combinations of various pathogens (page 22 lines 5-8). Barenkamp et al., specifically teaches that vaccines which contain antigenic material of several pathogens are combined vaccines and also belong to the present invention (page 22 lines 5-8)."

The passage in question describes the possibility of having vaccines containing

> "... materials from various pathogens or from various strains of the same pathogen, or from combinations of various pathogens."

This passage is but a statement of the possibility of combining other antigens with the HMW protein in a vaccine composition. This passage contains no suggestion to <u>select</u> the mutant Hin47 protein for combination with HMW protein.

Based on this paucity of disclosure, at least part of which has clearly been misinterpreted by the Examiner, the Examiner concludes:

> "Therefore it would have been obvious at the time of applicant's invention to have an immunogenic composition to confer protection against *Haemophilus influenza* comprising at least two different antigens, where one is a high molecular weight adhesin protein, HMW1 or HMW2, since Barenkamp et al. (WO 97/36,914), teaches that adhesin proteins are potentially important protective antigens which should comprise one component of a multi-component non-typeable *H. influenzae* vaccine and the other component as taught by Loosmore et al., is an analog of Hin47 because Hin47 is a non-proteolytic heat shock protein which substantially reduced in proteolytic activity and can be used as an antigen and be included in other immunogenic preparations."

There is no indication in Barenkamp et al that:

> "Barenkamp et al ... teaches that adhesin proteins are potentially important protective antigens which should comprise <u>one component of a multi-component non-typeable *H. influenzae* vaccine</u>" (emphasis added).

Where is the statement in Barenkamp et al to provide a multi-component non-typeable *H. influenzae* vaccine? Clearly there is none. In addition, there is no indication in Barenkamp et al that:

> "Barenkamp et al ... teaches ... the other component as taught by Loosmore et al is an analog of Hin47"

Where is the statement in Barenkamp et al that, in the non-disclosed multi-component non-typeable *H. influenzae* vaccine, a non-proteolytic analog of Hin47 which is not an adhesin should be selected for such multi-component vaccine? Clearly there is none. The combination of cited prior art lacks any motivation whatsoever to select the mutant Hin47 protein of Loosmore et al and combine it with the HMW protein.

In addition, there is a clear lack of any motivation whatsoever to provide a composition comprising an HMW protein and a non-proteolytic analog of Hin47 in which the quantity of HMW protein present enhances the immunogenicity of the already highly immunogenic non-proteolytic analog of Hin47 protein, as recited in claim 7.

In addition, an important consideration when combining antigens in an immunogenic composition, is the possibility of impairing or adversely affecting the respective immunogenicities. In fact, applicants data showed antigenic interference for certain doses and an enhancing effect under other doses (see page 12, line 13 to page 13, line 9). In addition, at dose levels where the HMW and Hin47 proteins did not impair their respective immunogenicities, formulating such components with DTP-polio-PRP-T vaccine did not result in any significant synergistic or suppressive effect on the additional antigens (see page 14, lines 10 to 23). Such results could not have been predicted in advance from the information provided in Barenkamp et al and Loosmore et al.

Accordingly, a person skilled in the art would not know ahead of time, assuming he were to select the non-proteolytic analog of Hin47 to combine with HMW protein, a motivation which, it is submitted, is completely lacking in the art, whether or not the proteins were combinable into an effective multi-component immunogenic composition.

In the Final Action, the Examiner attempts to address the lack of motivation to select mutant Hin47 to combine with HMW protein in an immunogenic composition and further states:

> "Both Barenkamp et al. (WO 97/36,914), and Loosmore et al., teach the use of adjuvants, the addition of other additional antigenic components and methods for immunizing a host against disease caused by an infection with *H. influenzae* comprising administration of the composition."

The teachings of Barenkamp et al with respect to "other antigenic component" has been discussed above. Adjuvants are commonly used in immunogenic compositions intended for vaccine use and hence their recitation in Barenkamp et al and Loosmore et al is hardly surprising, but totally irrelevant to any motivation to select a non-proteolytic analog of Hin47, as described by Loosmore et al, to provide a multi-component immunogenic composition as defined by applicants claims.

In the Office Action, the Examiner points to no specific teaching of Loosmore et al to support the suggestion that Loosmore et al teach the addition of the additional antigenic material. However, the following passages may be found in Loosmore et al:

> "The immunogenic compositions of the invention may further comprise at least one other immunogenic or immunostimulating material such as an adjuvant" (col. 3, ll. 63 to 66)

> "Variants which contain antigenic material of several pathogens are combined vaccines and also belong to the present invention. Such combined vaccines contain ... material from various pathogens or from various strains of the same pathogen, or combinations of various pathogens" (col. 9, ll. 10 to 19).

It is assumed that these are the passages on which the Examiner relies. However, it can be seen that they are no more relevant than the vague generalities contained in Barenkamp et al with respect to additional components. Yet, on the basis of these teachings, the Examiner asserts in the Final Action:

> "Thus, applicants argument that because is no suggestion to combine a HMW protein and the Hin47 because neither protein is specifically recited is not persuasive."

It is again urged that there is no motivation provided from the disclosure of Barenkamp et al to select the non-proteolytic analog of Hin47 protein, as described by Loosmore et al from the myriad of possibilities for "additional antigen

components" and combine that specifically-selected material with the HMW protein. In addition, there is no motivation to select the non-proteolytic analog of Hin47 protein for the purpose that the applicants make the selection.

The Examiner concludes:

> "It would have been obvious at the time of applicant's invention to have an immunogenic composition which confers protection against *Haemophilus influenzae* comprising at least two different antigens, where at least one of the antigens is an adhesin and the other antigen is not an adhesin as taught by Barenkamp et al. (WO 97/36,914), in view of Loosmore et al."

It is once again pointed out that there is no specific teaching in Barenkamp et al to provide an immunogenic composition which confers protection against *Haemophilus influenzae* comprising at least two different antigens, where at least one of the antigens is an adhesin and the other antigen is not an adhesin, no matter how hard the Examiner may wish it were so.

The Examiner goes on in the Final Action:

> "Loosmore et al., teaches that adhesin proteins are potentially important protective antigens which should comprise other immunostimulating components; the Hin47 antigen is immunogenic because it stimulates an immune response, can confer protection against diseases caused by a bacterial pathogen, including *Haemophilus influenzae;* and may immunogenic composition may further comprise at least one other immunogenic or immunostimulating material."

These disclosures of Loosmore et al provide no motivation whatsoever to select a non-proteolytic Hin47 which is not an adhesin for combination with the HMW protein of Barenkamp et al.

The Examiner's rejection herein does not take into account the reason why applicants combine these two proteins, as set forth in the Background to the Invention section of the specification. The applicants are striving to develop a vaccine intended to be effective against otitis media caused by *Haemophilus influenzae*.

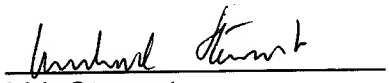
Barenkamp et al had isolated and characterized the HMW protein, which is a high molecular weight outer membrane protein of non-typeable strains of *Haemophilus influenzae*. These proteins were found to be adhesins and prevent establishment of nasopharyngeal colonization by *H. influenzae*. However,

applicants have found that the HMW are not present in all encapsulated (non-typeable) strains of *H. influenzae* but rather in about 75% of NTHi strains. Accordingly, to provide a better coverage against disease and a broad spectrum of disease protection, it is desirable to provide an additional protective antigen found in all *H. influenzae* strains. The latter protein is Hin47 protein employed herein, in the form of a non-proteolytic analog.

Having regard to the above, it is submitted that claims 1 to 24 are patentable over the applied art and hence the rejection thereof under 35 USC 103(a) as being unpatentable over Barenkamp et al in view of Loosmore et al, should be withdrawn.

It is believed that this application is now in condition for allowance and early and favourable consideration and allowance are respectfully solicited.

Respectfully submitted,



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